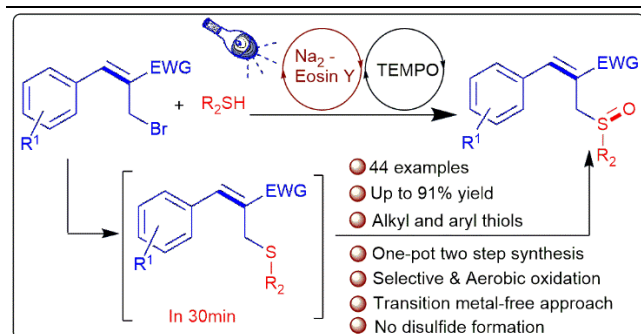


One-pot Chemo Selective Aerobic Cascade Synthesis of Allyl-Aryl Sulfoxides Enabled by Photoinduced Na₂ - Eosin Y and TEMPO

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Allylic sulfoxides are ubiquitous in medicine and catalysis. Chemo-selective synthesis of allyl-aryl sulfoxides are challenging as competitive isomerization, over oxidation of allylic C-H as well as sulfur. Herein, we have accomplished an unprecedented, metal-free one-pot protocol for the exclusive synthesis of allyl-aryl sulfinyls from Morita–Baylis–Hillman allyl bromides and thiols under visible light photocatalysis through a radical process. The highlight of this process is the selective and controlled oxidation of in situ formed allyl-aryl sulfides by merging sub-stoichiometric oxidizing agent TEMPO and visible light photocatalysis where overoxidation was completely excluded. This approach provides an efficient one-step access to biologically relevant and synthetically important molecules.

Introduction

Sulfoxides are major class of organosulfur compounds¹ used as chiral auxiliaries, intermediates in construction of heterocyclic architectures,² pummerer-based transformations,³ coupling reactions,⁴ sigmatropic rearrangements,⁵ most recently in radical transformations, etc.⁶ Moreover, sulfoxides display a widespread spectrum of applications in electrochemistry,⁷ agrochemicals⁸ as well as in medicinal chemistry. Notably, Sulindac (anti-inflammatory), Omeprazole (anti-ulcer), Modafanil (anti-psychotics), etc are few marketed sulfoxides drugs and Alliin, isolated from garlic, helps to promote glucose metabolism, prevent heart attacks and insulin sensitivity.⁹ Also, allylic sulfoxides are active against NLRP₃ inflammasome¹⁰ and are valuable targets by virtue of its significant transformability.

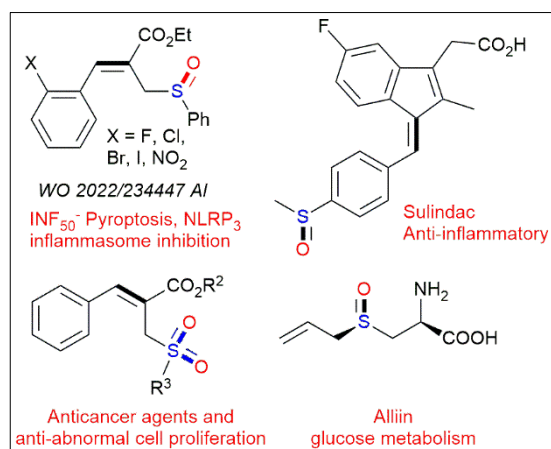
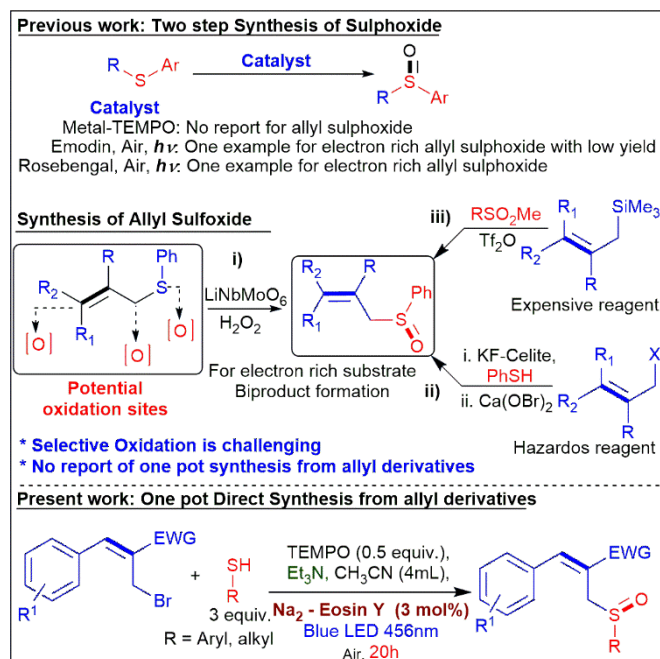


Figure. 1 Selected representatives of bioactive sulfoxides

Past few decades have witnessed a multitude of sulfinylation approaches via nucleophilic, electrophilic, radical as well as sulfide oxidation using various sulphur precursors under thermal and photosensitisation.¹¹ By merging transition metal catalysis and stoichiometric oxidants like 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO), aryl-alkyl sulphides are known to form sulfoxides under aerobic condition.¹² Thiols under aforementioned condition forms disulphides.¹³ Nevertheless, conventional methods for chemo-selective oxidation of allyl sulfides to allyl-aryl sulfoxides encounters challenges of completing allylic oxidation, isomerization, radical coupling, aldehyde, epoxidation and sulfone formation. In 2001, allylic sufoxidation of electron rich system was achieved by Khoo et al. with stoichiometric hydrogen peroxide using metal oxide composite, LiNbMoO₆, as catalyst (scheme 1. i) where sulfone was formed as a biproduct.¹⁴ In 2012, Vittorio and co-workers disclosed selective oxidation of aryl-allylic sulfides (scheme 1. ii) using hazardous calcium hypobromite in stoichiometric amount.¹⁵ Allyl derivatives, a better synthon for allylic sulfoxides, are seldom explored in this direction. Yoshida and co-workers have disclosed the synthesis of allyl-aryl sulfoxides from expensive allyl silanes and sulfonate esters through an interrupted pummerer reaction in 2020 (scheme 1. iii).¹⁶ Nevertheless, existing approaches relay on transition metal catalysis, stoichiometric use of hazardous oxidants, multistep approach or expensive reagents that often leads to overoxidation. Hence, a non-hazardous, non-expensive, less reactive yet oxidising condition for the selective and controlled synthesis of allyl-aryl sulfoxides are highly sought for. In this context, Morita-Baylis-Hillman (MBH) adducts¹⁷, and its derivatives have been widely used as the multifunctional allylic synthons.¹⁸ Although, MBH adducts,¹⁹ acetates²⁰ and bromides²¹ are well explored for thiolation,

sulfonation and their further transformations under photochemical²² and thermal²³ conditions, a chemo-selective and organo catalytic photoinduced synthesis of allyl sulfoxides is still elusive.



Scheme. 1 Strategies for the synthesis of allyl-aryl sulfoxides.

Recently, visible light mediated organo-photo catalysis²⁴ is emerging as a blueprint for redox²⁵, hydrogen atom transfer²⁶ and energy transfer²⁷ processes owing to its tuneable redox characteristics. Hence, we presumed that merging organo-photo catalysis with sub-stoichiometric oxidants under aerobic condition could offer an ideal one pot system for the controlled conversion of MBH allyl derivatives allylic sulfoxides. To the best of our knowledge, a direct organo photocatalytic one pot selective synthesis of allyl-aryl sulfoxides from allyl bromides, devoid of overoxidation and functional group tolerance, has not been reported yet. This led us to explore the possibility of a metal-free organo photocatalytic approach for the tandem synthesis of allyl-aryl sulfenyls from MBH allyl bromides and thiols using non-expensive xanthene dyes.

Results and discussion

We began our study by irradiating a mixture of one equiv. of ethyl (Z)-2-(bromomethyl)-3-phenylacrylate (**1a**), Et₃N (1 equiv.), TEMPO (0.5 equiv.), thiophenol (**2a**, 3 equiv.) and Na₂-Eosin Y (3 mol%) as a photocatalyst in 4 mL of acetonitrile with 456 nm Blue LED. To our delight, ethyl (Z)-3-phenyl-2-((phenylsulfinyl)methyl)acrylate (**3a**) was obtained as anticipated in 91% in 20 hours (Table 1, entry 1) as the product and less than 1% of S-phenyl benzenesulfinothioate (**3a'**) as confirmed by NMR) as by-product. Satisfyingly, there were no overoxidation, isomerization and aldehyde formation. The structure of **3a** was confirmed by ¹H, ¹³C, NOESY, HSQC - NMR and HRMS. Reaction in the absence of light as well as photocatalyst yielded only **3a''** in 85% yield (Table 1, entry 2). Without photocatalyst, the yield of **3a** is reduced to 4% with 80% of **3a''** (Table 1, entry 3). This ensures the role of light and Na₂-Eosin Y for effecting the cascade synthesis

of allyl aryl sulfoxides. The role of base was ensured by conducting the reaction without base resulted in unreacted **1a** (Table 1, entry 4). When the reaction was conducted in the absence of TEMPO, the formation of **3a** was diminished to 69% with a slight escalation in the yield of benzenesulfinothioate to 5% (Table 1, entry 5). The **3a** yield was found to be reduced to 83%, when the stoichiometry of TEMPO increased to 1 equiv. (Table 1, entry 6). Therefore, TEMPO stoichiometry is crucial to increase the yield of **3a**.

Table 1. Optimization of reaction conditions.

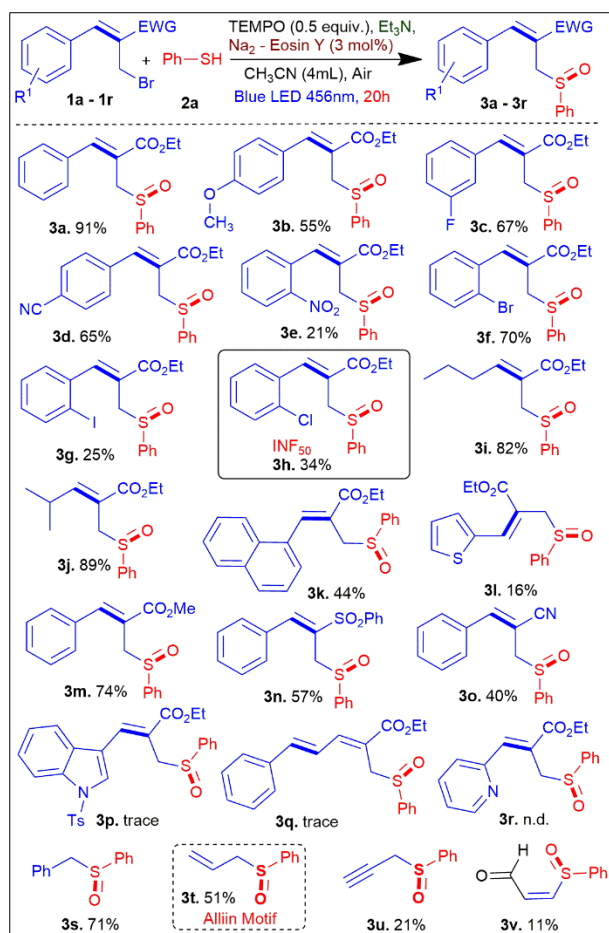
| S. No | Deviation from std. condition | t (h) | Yield ^a (%) | | |
|----------------|---|-------|------------------------|-------|-------|
| | | | 3a | 3a' | 3a'' |
| 1 | None | 20 | 91 ^b | trace | 0 |
| 2 ^c | No light, No PC | 20 | 0 | 0 | 85 |
| 3 | No PC | 20 | 4 | trace | 80 |
| 4 | No Et ₃ N | 20 | 0 | 0 | 0 |
| 5 | No TEMPO | 20 | 69 | 5 | trace |
| 6 | TEMPO 1 equiv. | 20 | 83 | trace | 0 |
| 7 | None | 1 | 0 | 0 | 95 |
| 8 | None | 12 | 64 | trace | 31 |
| 9 | None | 18 | 89 | trace | 0 |
| 10 | Ar atm. | 20 | 50 | trace | trace |
| 11 | White LED | 20 | trace | trace | 90 |
| 12 | Green LED | 20 | 80 | trace | trace |
| 13 | Sunlight | 7 | 49 | trace | 21 |
| 14 | Eosin Y | 20 | 75 | trace | 17 |
| 15 | Other Fluorescein dyes | 20 | 0-50 | trace | trace |
| 16 | TEOA 1 equiv. | 20 | 0 | 0 | 90 |
| 17 | TMEDA 1 equiv. | 20 | 80 | trace | trace |
| 18 | DABCO 1 equiv. | 20 | 51 | trace | trace |
| 19 | K ₂ S ₂ O ₈ 0.5 equiv. | 20 | 49 | trace | 36 |
| 20 | H ₂ O ₂ 0.5 equiv. | 20 | 31 | trace | trace |
| 21 | CH ₃ CN: H ₂ O | 20 | 78 | trace | trace |
| 22 | Benzoic acid 1 equiv. | 20 | 70 | trace | 0 |
| 23 | None | 20 | 71 ^d | 16 | 0 |

^a Isolated yield ^b Optimized reaction condition : **1a** (0.111 mmol), **2a** (3 equiv.), Et₃N (1 equiv.), TEMPO (0.5 equiv.), P.C (3 mol %), CH₃CN (4 mL), rt, Open atm., Blue LED 456 nm (40 W), 20 h; ^c thermal condition; ^d 3.71 mmol of **1a** (Gram scale)

1a was completely consumed in 1 hour with only **3a''** being formed in 95% (Table 1, entry 7). The reaction in 12 hours yielded **3a** and **3a''** in 64% and 31% whereas in 18 hours, only **3a** was formed in 89% exclusively (Table 1, 8 & 9). The reaction under argon atmosphere diminished the yield of **3a** to 50% (Table 1, entry 10) indicating the necessity of aerobic oxygen for the formation of **3a**. Attempt to conduct the reaction in white light resulted in allyl sulphide intermediate **3a''** only in 90% whereas green light and sunlight yielded **3a** in 80%, and 49% respectively (Table 1, entries 11 to 13). When Na₂-Eosin Y was replaced with Eosin Y, Rose bengal,

Rhodamine-6G and Fluorescein, the results were inferior (Table 1, entries 14 & 15). Among various bases, TEOA failed to give **3a** whereas TMEDA diminished desired product to 80% (Table 1, entries 16 to 17). Presence of DABCO, a singlet oxygen quencher, reduces the yield to 51% (Table 1, entries 18) confirming the role of singlet oxygen during the cause of reaction. Replacing TEMPO with potassium persulfate and hydrogen peroxide did not create much impact on yield of **3a** (Table 1, entries 19 & 20).

Table 2. Substrate scope of Morita-Baylis-Hillman (MBH) allyl-aryl bromides with thiophenol via photochemical condition.^a



^a Reaction condition - **1a** (0.111 mmol), **2a** (3 equiv.), **Et₃N** (1 equiv.), **TEMPO** (0.5 equiv.), **P.C** (3 mol %), **CH₃CN** (4 mL), rt, Open atm., Blue LED 456nm (40 W), 20 h; ^b Isolated yield; **3a'** – trace amount in all the cases.

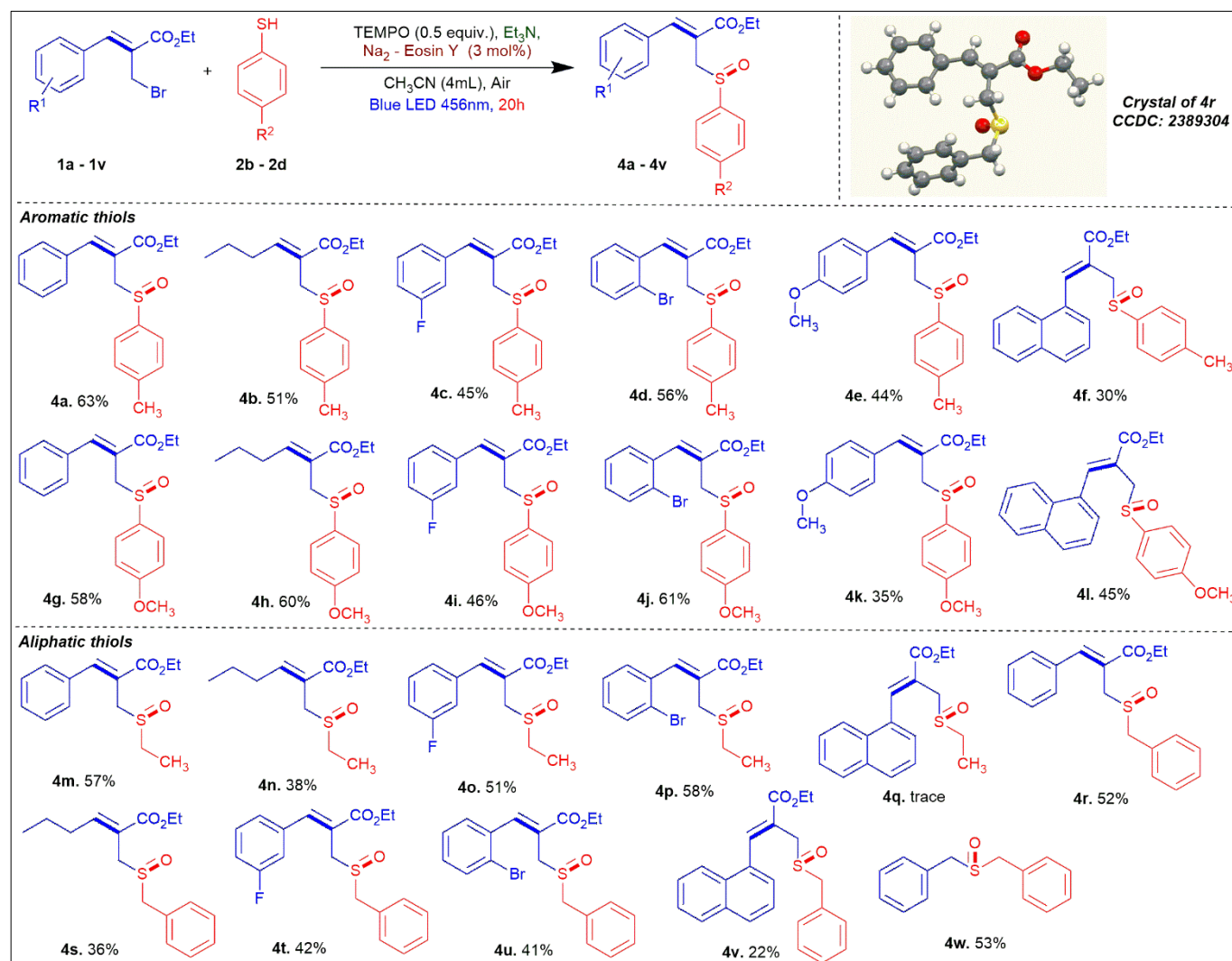
Other solvents like dimethyl sulfoxide (DMSO), dimethyl- formamide (DMF), ethanol, DCM, methanol, tetrahydrofuran (THF) and water (H₂O) were screened to compare the reaction but failed to give the productive yields (**ESI**). We also checked the reactivity in CH₃CN: H₂O (3:1mL) mixture. The expected product is reduced to 78% (Table 1, entry 21). The effect of acid by using benzoic acid was also checked (Table 1, entry 22) and the yield of **3a** was diminished to 70%. MBH

alcohol instead of MBH bromides failed to give the product while the corresponding acetate gave 26% yield. Detailed optimization table can be seen in **ESI**.

Encouraged by the initial results, we sought to determine the substrate scope of the reaction. Different aryl, heteroaryl and alkyl substituted allyl bromides were employed under the optimized condition with thiophenol (**2a**) and the results were shown in **table 2**. The position and electronic effect of substituents on the phenyl ring of allyl bromides had a negligible influence on the overall transformation and observed moderate to good yields (**3a-3h**, 25 to 91%). Notably, even strong electron-withdrawing groups such as cyano and nitro (**3d** & **3e**, 65% and 21%) gave the sulfoxides albeit in good yield. Out of all allyl-aryl sulfoxides synthesized, **3h** ((Z)-ethyl 3-(2-chlorophenyl)-2-((phenylsulfinyl)methyl) acrylate - **INF50**),^{10b} is known to display pyroptosis and inhibitory activity against the NLRP₃ inflammasome. Furthermore, non-aromatic allyl bromides (**3i** & **3j**, 82% & 89%) were found to be well-tolerated to the reaction condition, greatly enhancing the synthetic utility of this methodology. Polyaromatic and heteroaromatic substituted allyl bromides were also compatible with the one-pot selective oxidation condition (**3k** & **3l**, 44% & 16%). Additionally, even allyl bromides with highly electron withdrawing cyano and phenyl sulfone groups gave moderate to good yields (**3n** & **3o**, 40% & 57%). Unfortunately, conjugated allyl bromides with N-tosyl indole and 2-Aryl vinyl substituted allyl bromides gave product in trace quantity as confirmed by HRMS (**3p** & **3q**) whereas 2-pyridyl allyl bromide failed to give desired product (**3r**). We examined the applicability of the developed methodology to benzyl bromide and unsubstituted allyl bromide and observed the corresponding (benzylsulfinyl)benzene (**3s**) in 71% yield, (allylsulfinyl) benzene (**3t**, alliin motif) in 51% yield. Propargyl bromide afforded a mixture of (prop-2-yn-1-ylsulfinyl) benzene (**3u** in 21% yield) and (Z)-3-(p-methoxyphenylsulfinyl)acrylaldehyde (**3v** in 11% yield) as by-product.

Next, we sought to extend the compatibility check of the developed protocol by employing various other substituted aromatic as well as aliphatic thiols in **table 3**. Reaction of p-thiocresol with different MBH allyl bromides gave products **4a – 4f** in 30% to 63% yields whereas 4-methoxy benzenethiol yielded the corresponding sulfoxides **4g – 4l** (35% to 61%). Additionally, it is worth noticing that ethyl mercaptan was found to be well tolerated to the standard condition yielding the allyl-alkyl sulfoxides in moderate to good yields (**4m – 4p**, 38% to 58%) except for polyaromatic derivative (**4q**). Benzyl mercaptan afforded the desired products (**4r – 4v**, 22 to 42%) in moderate yields. The structure of **4r** was also confirmed by single crystal XRD analysis (**ESI**). Simple benzyl bromide with Benzyl mercaptan gave the product (sulfinylbis(methylene))dibenzene (**4w**, 53%) in one-pot synthesis. Further the reaction was scaled up to 3.71 mmol and **3a** was produced in 71 % yield and **3a'** in 16 % yield (see **ESI**, **Sec 6**).

To understand a possible reaction mechanism, several control experiments were performed (Table 4). The HRMS and NMR analysis

Table 3. Substrate Scope of different thiol derivatives for synthesis of allyl-aryl sulfoxides.^a

^a Reaction condition - **1a** (0.111 mmol), **2b - d** (3 equiv.), **Et₃N** (1 equiv.), **TEMPO** (0.5 equiv.), **P.C** (3 mol %), **CH₃CN** (4 mL), rt, Open atm., Blue LED 456nm (40 W), 20 h.

of the crude reaction mixture quenched after 1 hour, (Table 4, entry 1) confirm the formation of (Z)-ethyl 3-phenyl-2-((phenylthio)methyl) acrylate (**3a''**) convincing that the reaction proceeds via two-step in one-pot. Increasing the stoichiometry of TEMPO from 0.5 equiv. to 1.5 equiv. from the standard condition completely suppressed the yield of (Z)-ethyl 3-phenyl-2-((phenylsulfinyl)methyl) acrylate (**3a**), and stopped the reaction at the sulfide **3a''** formation step (Table 4, entry 2). HRMS analysis of the crude reaction mixture revealed the formation of TEMPO adduct of thiol radical at *m/z* 266.1572 ([*M*+*H*]) for TEMPO-SPh as well as *m/z* 456.2576, [*M*+*H*] for TEMPO-**3a**-H, indicating the radical intermediary during the reaction. Quenching experiments with DABCO (2 and 4 equiv.) reduced the yield **3a** to 27% and 0% respectively (Table 4, entries 3 & 4) signifies the role of singlet reactive oxygen species in the reaction. Replacing TEMPO with 0.5 equiv of butylated hydroxytoluene (BHT) (Table 4, entry 5), resulted in reduction in the yield of **3a** to 71% further confirms the radical formation. Further, performing the reaction with intermediate **3a''** (Table 4, b) employing standard condition yielded **3a** in 59% with

unreacted **3a''**. Whereas without photocatalyst, the yield of **3a** (1%) was suppressed completely. This concludes the role of photocatalyst in sulphide oxidation. In order to find the effect of bromide as a counter ion, the reaction **3a''** under optimized condition was done with KBr and TBAB (Table 4, b) and found that yield of **3a** was increased. In contrast to the earlier reports of TEMPO mediated disulfides formation,¹³ thiol under standard condition remains intact (Table 4, c) confirming the formation of **3a'** is not directly from the thiol.

Comparing the slopes of the Stern-Volmer quenching plots revealed that photoluminescence of Na₂-Eosin Y was mainly quenched by TEMPO (Slope = 0.2657) than **3a''** (Slope = 0.1664), **1a** (Slope = 0.1392), thiophenol (**2a**, Slope = 0.0529) and Et₃N (Slope = 0.0296) which imply the reaction proceeded through reductive quenching of the PC by TEMPO (Figure 2). In the absence of TEMPO, **3a''** can be involved in the reductive quenching of the excited photocatalyst. Detailed quenching studies can be seen in ESI.

Table 4. Control Experiments.

a)

Std. Cond.: TEMPO (0.5 equiv.), Et₃N, Na₂-Eosin Y (3 mol%), CH₃CN (4mL), Air, Blue LED 456nm, 20h

| S.No. | Deviation from the Std.condition | Time (h) | Yield 3a | Yield 3a' | Yield 3a'' |
|-------|----------------------------------|----------|----------|-----------|------------|
| 1 | None | 1 | 0% | 0% | 95% |
| 2 | TEMPO 1.5 equiv. | 20 | 0% | trace | 31% |
| 3 | DABCO 2 equiv. | 20 | 27% | 0% | 95% |
| 4 | DABCO 4 equiv. | 20 | 0% | 0% | 0% |
| 5 | BHT 2 equiv | 20 | 71% | trace | trace |

b)

| Deviation from the Std.condition | Yield (3a) ^a | Yield (3a') |
|-----------------------------------|-------------------------|-------------|
| None | 59 % (71%) | 0% |
| Without PC | 1 % (86%) | 0% |
| With thiophenol 2a and without PC | trace | 0% |
| With KBr | 73% (81%) | 0% |
| With TBAB | 63% (71%) | 0% |

^a:Recovered yields are mentioned in parenthesis

c)

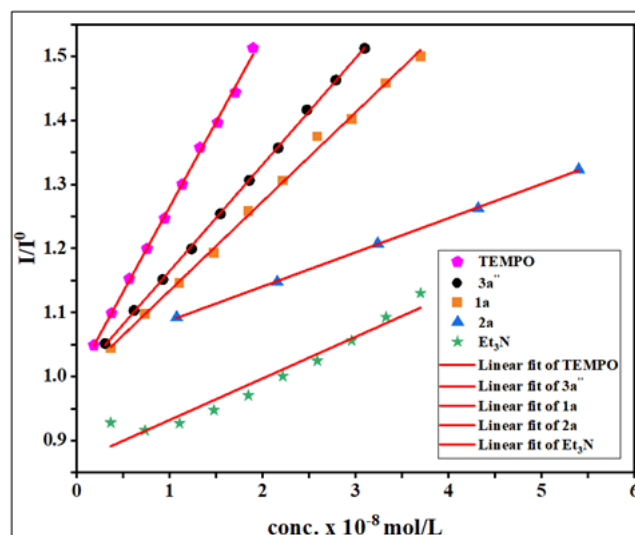
R = Ph-H, Ph-OCH₃

0% (3a') 0%

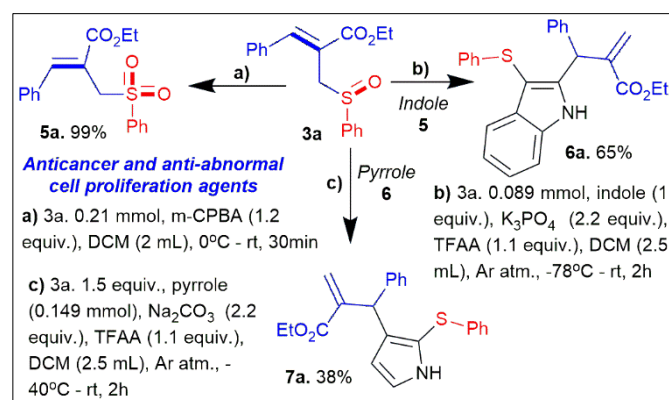
Implication:

a). The reaction did not proceed through disulfide formation
 b). 3a' is not directly formed from thiol radical

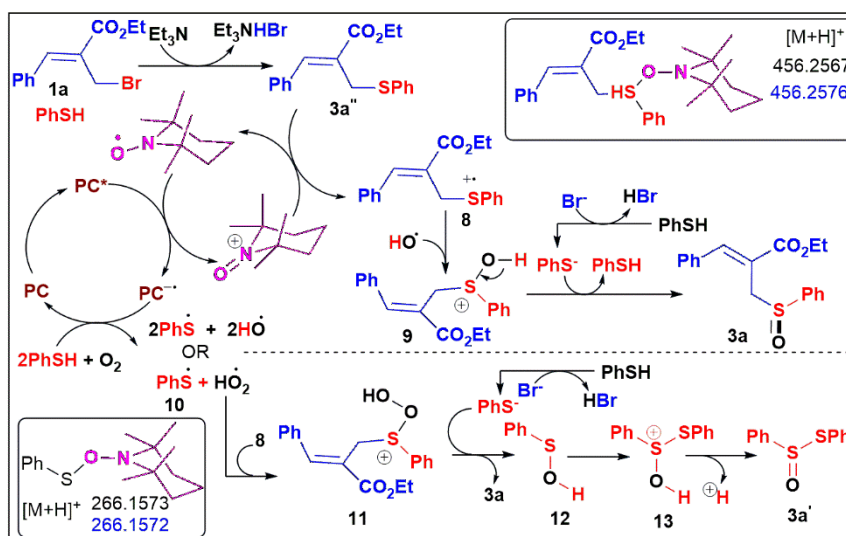
Based on the control experiments, quenching, Stern–Volmer studies, crude HRMS analysis and literature studies²⁸, we proposed the plausible mechanisms in **Scheme 3**. The initial event is the formation of the allyl-aryl sulfide **3a''** from **1a** and thiol in presence of Et₃N. In presence of TEMPO,^{28a,b} the reaction is initiated by photoexcitation of the photocatalyst(PC) by visible light to give the corresponding excited PC*, which then undergoes reductive quenching by Single Electron Transfer (SET) from TEMPO to generate highly reducing PC^{•-} along with a specific and strong oxidant, oxoammonium cation (TEMPO⁺). Thiol and dioxygen assisted regeneration of PC results in thiol radical and hydroxyl radical. TEMPO⁺ oxidizes **3a''** regenerating TEMPO and sulphide radical cation **8**. Hydroxyl radical combines with **8** forms an adduct **9** (HRMS confirmed) which forms **3a**. A less feasible pathway is also possible by the aerobic oxygen and thiol assisted regeneration of PC with the formation of Radical Oxygen Species (ROS), HO₂[•] and thiol radical (**10**). **8** and ROS recombines to form the intermediate **11** followed by an elimination of PhSOH (**12**) leading to the formation of **3a**. **12** reacts with thiol radical to form intermediate **13** on deprotonation yields traces of **3a'**.

**Figure 2.** Stern-Volmer Plot.

Having demonstrated the applicability of the developed methodology for the synthesis of various highly functionalized allyl-aryl sulfoxides, we ought to explore the functional transformations of the synthesized sulfoxides. Meta-chloroperbenzoic acid, mediated oxidation of methyl (Z)-3-phenyl-2-((phenylsulfinyl)methyl)acrylate (**3a**) yielded methyl (Z)-3-phenyl-2-((phenylsulfonyl)methyl)acrylate (**5a**), an anticancer and anti-abnormal cell proliferation agents, in 99% yield. Indolyl aryl sulfides, sulfones and sulfoxides constitute a class of therapeutics targeting non-nucleoside reverse transcriptase inhibitors against Human Immunodeficiency Virus (HIV) type - 1.²⁹ An interrupted pummerer reactions of allyl-aryl sulfones with indole and pyrrole could enroute to indolyl-aryl sulfides. Thus, as a representative transformation, the reaction of methyl (Z)-3-phenyl-2-((phenylsulfinyl)methyl)acrylate (**3a**) with indole/pyrrole in presence of TFAA and base yielded the ethyl 2-(phenyl(3-(phenylthio)-1H-indol-2-yl)methyl)acrylate (**6a**) and ethyl 2-(phenyl(2-(phenylthio)-1H-pyrrol-3-yl)methyl)acrylate (**7a**) in 65% and 38% respectively.

Scheme 2. Application of the synthesized strategy and Synthetic transformations.

Scheme 3. Plausible reaction mechanism.



Conclusions

In conclusion, for the first time, we have accomplished a simple one-pot visible light mediated protocol for the selective and controlled synthesis of a library of allyl-aryl sulfinyls from Morita–Baylis–Hillman allyl-aryl bromide derivatives and thiols under aerobic condition. Eosin Y disodium salt is used as a photocatalyst, and TEMPO is used as a sub-stoichiometric oxidizing agent. A plausible radical mechanism is proposed with adequate supporting evidence by analysing the crude HRMS and control experiments. We have also demonstrated the application of the developed methodology for the synthesis of biologically relevant compounds with anticancer and anti-abnormal cell proliferation agent against the NLRP₃ inflammasome. In particular, the approach provides efficient one-step access to biologically relevant and synthetically important molecules.

Author contributions

The authors confirm the following contributions to this paper: study conception and design, B. V.; Methodology and experiments, B. T. and A. S.; Manuscript preparation, B. T. and B. V.

Conflicts of interest

The authors declare no competing financial interest.

Data availability

The data underlying this studies are available in the published article and its supporting information.

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